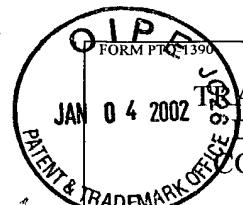


01-09-02

EXpress MAIL LABEL NO. EV020740978US  
 DATE OF DEPOSIT: 4 January 2002

JC10 Rec'd PCT/PTO 04 JAN 2002



U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. § 371		22-62030
INTERNATIONAL APPLICATION NO. PCT/CA00/00789	INTERNATIONAL FILING DATE 5 July 2000	U.S. APPLICATION NO. (If known, see 37 CFR § 15) 10/030973
TITLE OF INVENTION ELECTRICAL STIMULATION SYSTEM AND METHODS FOR TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB		
APPLICANT(S) FOR DO/EO/US Joaquin Andres Hoffer		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. § 371. 2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. § 371. 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. § 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. § 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19 <sup>th</sup> month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. § 371(c)(2)) a. <input checked="" type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> has been transmitted by the International Bureau c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. § 371(c)(2)). 7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. § 371(c)(3)) a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made, however, the time limit for making such amendments has NOT expired. d. <input checked="" type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. § 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. § 371(c)(4)) 10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. § 371(c)(5)). 		
Items 11. to 16. below concern document(s) or information included:		
11. <input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. §§ 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§ 3.28 and 3.31 and the Recordal fee of \$40.00 is included. 13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. <input type="checkbox"/> A <b>SECOND</b> preliminary amendment 14. <input type="checkbox"/> A substitute specification 15. <input type="checkbox"/> A change of power of attorney and/or address letter. 16. <input checked="" type="checkbox"/> Other items or information <input type="checkbox"/> Written Opinion. <input checked="" type="checkbox"/> Preliminary Examination Report. <input checked="" type="checkbox"/> International Search Report. <input type="checkbox"/> Copies of References Cited.		



24197

EXPRESS MAIL LABEL NO. EV020740978US

DATE OF DEPOSIT: 4 January 2002

JC13 Rec'd PCT/PTC 04 JAN 2002

U.S. APPLICATION NO. (If known, see 37 C.F.R. § 1.5)		INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
10/030973		PCT/CA00/00789	22-62030
17. <input checked="" type="checkbox"/> The following fees are submitted:		CALCULATIONS (PTO USE ONLY)	
<b>BASIC NATIONAL FEE (37 C.F.R. §§ 1.492(a)(1)-(5)):</b>			
Neither International Preliminary Examination fee (37 C.F.R. § 1.482) nor International Search fee (37 C.F.R. § 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO. .... \$1,040.00			
International Preliminary Examination fee (37 C.F.R. § 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO. .... \$890.00			
International Preliminary Examination fee (37 C.F.R. § 1.482) not paid to USPTO but International Search fee (37 C.F.R. § 1.445(a)(2)) paid to USPTO as an International Searching Authority. .... \$740.00			
International Preliminary Examination fee paid to USPTO (37 C.F.R. § 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4). .... \$710.00			
International Preliminary Examination fee paid to USPTO (37 C.F.R. § 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4). .... \$100.00			
<b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>			\$ 890.00
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. § 1.492(e)).			\$
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE
Total claims	19 - 20 =	0	x \$18.00 \$ 0.00
Independent Claims	3 - 3 =	0	x \$84.00 \$ 0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ \$280.00 \$
<b>TOTAL OF ABOVE CALCULATIONS =</b>			\$ 890.00
<input type="checkbox"/> Reduction of 1/2 for filing by small entity Small entity status is claimed for this application			\$
<b>SUBTOTAL =</b>			\$ 890.00
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 Months from the earliest claimed priority date (37 C.F.R. §§ 1.492(f)) +			\$
<b>TOTAL NATIONAL FEE =</b>			\$ 890.00
Fee for recording the enclosed assignment (37 C.F.R. § 1.21(h)) The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§ 3.28, 3.31). \$40.00 per property. +			\$
<b>TOTAL FEES ENCLOSED =</b>			\$ 890.00
			REFUND → \$
			CHARGE → \$

a.  A check in the amount of \$890.00 to cover the above fees is enclosed

b.  Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees A duplicate copy of this sheet is enclosed

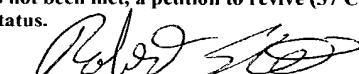
c.  The Director is hereby authorized to charge any additional fees that may be required, or credit any overpayment, to Deposit Account No. 02-4550 A duplicate copy of this sheet is enclosed.

d.  Please return the enclosed postcard to confirm that the items listed above have been received.

**NOTE:** Where an appropriate time limit under 37 C.F.R. § 1.494 or § 1.495 has not been met, a petition to revive (37 C.F.R. § 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

KLARQUIST SPARKMAN, LLP  
One World Trade Center, Suite 1600  
121 S.W. Salmon Street  
Portland, OR 97204-2988

  
SIGNATURE  
Robert F. Scotti  
NAME

39,830  
REGISTRATION NUMBER

cc: Docketing

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Joaquin Andres Hoffer

Art Unit:

International Application No. PCT/CA00/00789

Filed: January 4, 2002

For: ELECTRICAL STIMULATION SYSTEM AND  
METHODS FOR TREATING PHANTOM LIMB  
PAIN AND FOR PROVIDING SENSORY  
FEEDBACK TO AN AMPUTEE FROM A  
PROSTHETIC LIMB

Examiner: Not yet assigned

Date: January 4, 2002

BOX PATENT APPLICATION  
COMMISSIONER FOR PATENTS  
WASHINGTON, D.C. 20231

**FIRST PRELIMINARY AMENDMENT**

Prior to examination of the above-referenced application, please amend the application as follows:

**In the Specification:**

In accordance with 37 CFR § 1.121, Applicant submits the following clean specification paragraphs. A marked up version is attached hereto.

On page 1, after the title, please insert the following paragraph:

**--PRIORITY CLAIM**

This application is a § 371 U.S. national stage of PCT/CA00/00789 filed July 5, 2000, which was published in English under PCT Article 21(2), which in turn claims the benefit of U.S. Provisional Application 60/142,983 filed July 6, 1999.--

On page 2, line 6, amend paragraph as follows:

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as “cortical plasticity” (Ramachandran, V.S., and Hirstein, W. (1998). *The Perception of Phantom Limbs*. The D.O. Hebb lecture. *Brain* 121: 1603-1630), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. (1983) *Progression of Change Following Median Nerve Section in the Cortical Representation of the Hand in Areas 3b and 1 in Adult Owl and Squirrel Monkeys*. *Neuroscience* 10(3):639-65); (Kaas JH. (1998) *Phantoms of the Brain*. *Nature* 391(6665):331, 333) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs. .

On page 3, line 10, amend paragraph as follows:

An important landmark in the pain scientific literature is the work by Wall and Melzack, ((1965) *Pain Mechanisms: A New Theory*. *Science* 150(699):971-9), who in the 1960's proposed the “Gate Control Theory” of pain whereby activity in large diameter touch Ab nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller A $\delta$  and C fibers. Although this hypothesis remains controversial, it has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

On page 4, line 10, amend paragraph as follows:

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer, J.A., Stein, R.B. and Gordon, T.

(1979) *Differential Atrophy of Sensory and Motor Fibers Following Section of Cat Peripheral Nerves*. Brain Res. 178:347-361) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al ((1981) *The Effects of Axotomy on the Condition Action Potentials in Peripheral Sensory and Motor Nerve Fibres*. J. Neurol Neurosurg Psychiatry 44(6):485-96) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in CV. Thus, in amputated nerves, "large" and "small" nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

On page 5, line 2, amend paragraph as follows:

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston KE (1945) *Phantom Limb Syndrome. A Discussion of the Role of Major Peripheral Nerve Neuromas*. J. Neurosurgery 2:251-5).

On page 6, line 4, amend paragraph as follows:

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensation. Stein, R.B., Charles, D., Hoffer, J.A., Arsenault, J., Davis, L.A., Moorman, S. and Moss, B (1980) *New Approaches to Controlling Powered Arm Prostheses, Particularly by High Level Amputees*. Bull. Prosth. Re. 17:51-62, showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside

the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in amputees can survive for 30 years or longer in the absent of suitable connections to sensory end-organs.

On page 6, line 23, add the following paragraph:

Schulman (U.S. Patent No. 4,232,679) and Schwabe (WO 98/25552) describe systems for providing stimuli to human tissues, but do not have the advantages provided by the present invention.

On page 20, line 6, amend sentence as follows:

Such a pharmacological system 70, which includes catheters 25, is also shown in Figure 1.

**In the Claims:**

In accordance with 37 CFR § 1.121, Applicant submits the following clean set of all pending claims. A marked up version is attached hereto.

1. A system for alleviating phantom limb pain in an amputee having a limb stump, said system comprising:

a plurality of electrodes implanted in said limb stump, said electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, said electrodes when supplied with electrical current providing electrical stimulation to said nerve; and

an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

2. The system as claimed in claim 1 wherein said electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in said limb stump so as to circumferentially surround a portion of said nerve.

3. The system as claimed in claim 2 wherein said nerve cuff is multi-chambered, and wherein each of said electrodes is segregated into one chamber of said nerve cuff, each electrode thereby being placed in close proximity to a different portion of said nerve.

4. The system as claimed in claim 3 wherein said electrical signal generator is outside of the amputee's body.

5. The system as claimed in claim 4 wherein said signals generated by said signal generator are communicated by said generator to said electrodes non-electrically, at least in part.

6. The system as claimed in claim 5 wherein said signals generated by said signal generator are communicated telemetrically across the skin of the amputee.

7. The system as claimed in claim 6 wherein said signal generator is contained within a prosthetic limb fashioned to replace the amputee's amputated limb.

8. The system as claimed in claim 7 wherein said prosthetic limb further comprises a plurality of sensors, each of which provides a sensor signal to said signal generator.

9. The system as claimed in claim 8 wherein said signals produced by said generator are responsive to signals produced by said sensors.

10. The system as claimed in claim 9 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

11. A method for alleviating phantom limb pain in an amputee, comprising the steps of:

(a) equipping an amputee with the system claimed in claim 1; and  
(b) providing a stream of nerve stimulation signals to alleviate phantom limb pain, thereby providing a flow of sensory traffic to the cortex.

12. A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, said system comprising:

(a) a prosthetic limb having a plurality of sensors, each sensor capable of sensing states of touch, or pressure, or force, or slip, or joint position or temperature, each of said sensors producing a unique sensor signal indicative of a sensed state;  
(b) a signal transducer contained within said prosthetic limb for transducing each of said unique sensor signals into a unique electrical signal suitable for stimulating action potential activity in nerve fibers;  
(c) A multi-chambered nerve cuff implanted in said limb stump, said cuff surrounding a severed sensory nerve in said limb stump and incorporating a plurality of electrodes, each of said electrodes when supplied with electrical current providing electrical stimulation to a portion of said nerve; and

(d) means for communicating each of said unique electrical signals to a predetermined electrode in said nerve cuff.

13. The system as claimed in claim 12 wherein said means for communicating said unique electrical signals comprises electrical and non-electrically signal transmission in combination.

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.

15. The system as claimed in claim 14 wherein a plurality of unique electrical signs are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.

17. The system as claimed in claim 12 comprising a plurality of nerve cuffs, each one surrounding a different nerve.

18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:

- (a) equipping an amputee with the system claim 12; and
- (b) providing sensory stimuli to said prosthetic limb.

19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:

a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person, said electrodes when supplied with

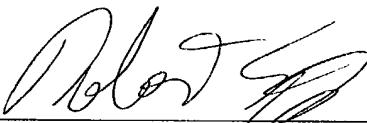
electrical current providing electrical stimulation to said nerve intermediate the site of injury of said nerve and the cortex; and

an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By



\_\_\_\_\_  
Robert F. Scotti  
Registration No. 39,830

One World Trade Center, Suite 1600  
121 S.W. Salmon Street  
Portland, Oregon 97204  
Telephone: (503) 226-7391  
Facsimile: (503) 228-9446

**Marked-up Version of Amended Claims and Specification  
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)**

**In the Specification:**

On page 1, after the title, please insert the following paragraph:

**-PRIORITY CLAIM**

This application is a § 371 U.S. national stage of PCT/CA00/00789 filed July 5, 2000, which was published in English under PCT Article 21(2), which in turn claims the benefit of U.S. Provisional Application 60/142,983 filed July 6, 1999. --

On page 2, line 6, amend paragraph as follows:

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as “cortical plasticity” (Srinivasan et al, 1991), (Ramachandran, V.S., and Hirstein, W. (1998). *The Perception of Phantom Limbs*. The D.O. Hebb lecture. Brain 121: 1603-1630), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich et al, 1983; Kaas, 1998) (Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. (1983) *Progression of Change Following Median Nerve Section in the Cortical Representation of the Hand in Areas 3b and 1 in Adult Owl and Squirrel Monkeys*. Neuroscience 10(3):639-65); (Kaas JH. (1998) *Phantoms of the Brain*. Nature 391(6665):331, 333) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs.

On page 3, line 10, amend paragraph as follows:

An important landmark in the pain scientific literature is the work by Wall and Melzack, ((1965) *Pain Mechanisms: A New Theory*. Science 150(699):971-9), who in the 1960’s proposed the “Gate Control Theory” of pain whereby activity in large diameter touch Ab nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller A $\delta$  and C fibers. Although this hypothesis remains controversial, it

has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

On page 4, line 10, amend paragraph as follows:

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer et al., 1979) (Hoffer, J.A., Stein, R.B. and Gordon, T. (1979) *Differential Atrophy of Sensory and Motor Fibers Following Section of Cat Peripheral Nerves*. Brain Res. 178:347-361) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al ((1981) The Effects of Axotomy on the Condition Action Potentials in Peripheral Sensory and Motor Nerve Fibres. J. Neurol Neurosurg Psychiatry 44(6):485-96) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in CV. Thus, in amputated nerves, “large” and “small” nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

On page 5, line 2, amend paragraph as follows:

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the

effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston, KE (1945) *Phantom Limb Syndrome. A Discussion of the Role of Major Peripheral Nerve Neuromas.* J. Neurosurgery 2:251-5).

On page 6, line 4, amend paragraph as follows:

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensation. [Stein et al. \(1980\)](#)

Stein, R.B., Charles, D., Hoffer, J.A., Arsenault, J., Davis, L.A., Moorman, S. and Moss, B (1980) New Approaches to Controlling Powered Arm Prostheses, Particularly by High Level Amputees. Bull. Prosth. Re. 17:51-62, showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in amputees can survive for 30 years or longer in the absent of suitable connections to sensory end-organs.

On page 6, line 23, add the following paragraph:

Schulman (U.S. Patent No. 4,232,679) and Schwabe (WO 98/25552) describe systems for providing stimuli to human tissues, but do not have the advantages provided by the present invention.

On page 20, line 6, amend sentence as follows:

Such a pharmacological system ~~60~~ 70, which includes catheters 25, is also shown in Figure 1.

### **In the Claims:**

1. A system for alleviating phantom limb pain in an amputee having a limb stump, said system comprising:
  - a plurality of electrodes implanted in said limb stump, said electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, said electrodes when supplied with electrical current providing electrical stimulation to said nerve; and
  - an electrical signal generator fashioned to communicate varying electrical signals to each electrode.
2. The system as claimed in claim 1 wherein said electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in said limb stump so as to circumferentially surround a portion of said nerve.
3. The system as claimed in claim 2 wherein said nerve cuff is multi-chambered, and wherein each of said electrodes is segregated into one chamber of said nerve cuff, each electrode thereby being placed in close proximity to a different portion of said nerve.
4. The system as claimed in claim 3 wherein said electrical signal generator is outside of the amputee's body.
5. The system as claimed in claim 4 wherein said signals generated by said signal generator are communicated by said generator to said electrodes non-electrically, at least in part.
6. The system as claimed in claim 5 wherein said signals generated by said signal generator are communicated telemetrically across the skin of the amputee.
7. The system as claimed in claim 6 wherein said signal generator is contained within a prosthetic limb fashioned to replace the amputee's amputated limb.

8. The system as claimed in claim 7 wherein said prosthetic limb further comprises a plurality of sensors, each of which provides a sensor signal to said signal generator.

9. The system as claimed in claim 8 wherein said signals produced by said generator are responsive to signals produced by said sensors.

10. The system as claimed in claim 9 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

11. A method for alleviating phantom limb pain in an amputee, comprising the steps of:

- (a) equipping an amputee with the system claimed in ~~any one of the claims~~ claim 1-10; and
- (b) providing a stream of nerve stimulation signals to alleviate phantom limb pain, thereby providing a flow of sensory traffic to the cortex.

12. A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, said system comprising:

- (a) a prosthetic limb having a plurality of sensors, each sensor capable of sensing states of touch, or pressure, or force, or slip, or joint position or temperature, each of said sensors producing a unique sensor signal indicative of a sensed state;
- (b) a signal transducer contained within said prosthetic limb for transducing each of said unique sensor signals into a unique electrical signal suitable for stimulating action potential activity in nerve fibers;
- (c) A multi-chambered nerve cuff implanted in said limb stump, said cuff surrounding a severed sensory nerve in said limb stump and incorporating a plurality of electrodes, each of said electrodes when supplied with electrical current providing electrical stimulation to a portion of said nerve; and
- (d) means for communicating each of said unique electrical signals to a predetermined electrode in said nerve cuff.

13. The system as claimed in claim 12 wherein said means for communicating said unique electrical signals comprises electrical and non-electrically signal transmission in combination.

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.

15. The system as claimed in claim 14 wherein a plurality of unique electrical signs are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.

16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.

17. The system as claimed in claim ~~10-12~~ comprising a plurality of nerve cuffs, each one surrounding a different nerve.

18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:

- (a) equipping an amputee with the system ~~claims in any one of the claims 12-17~~;
- (b) providing sensory stimuli to said prosthetic limb.

19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:

a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person, said electrodes when supplied with electrical current providing electrical stimulation to said nerve intermediate the site of injury of said nerve and the cortex; and

RFS.vjg 01/04/02 22-62030 91053  
PATENT

3 5 0 0 2 5 1 3 2 3 7 3 4 2  
EXPRESS MAIL LABEL NO. EV020740978US  
DATE OF DEPOSIT: January 4, 2002

an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

3/P&amp;D

ELECTRICAL STIMULATION SYSTEM AND METHODS FOR  
TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY  
FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB

5 Technical Field

This invention relates to a system and methods for electrical stimulation of body tissues, and more particularly to a system and methods for stimulating nerves to alleviate phantom limb pain in an amputee, and/or for providing sensory feedback from a prosthetic limb worn by an amputee.

10

Background

Limb amputations cause three major types of dysfunction. Two of these occur immediately, and are direct consequences of the amputation: the loss of motor function below the amputation level; and the 15 loss of all sensory feedback arising from the missing limb below the amputation level.

The third, more indirect dysfunctional consequence of amputation is that which is known as "phantom limb" sensations. These may occur either soon after, or at various delayed times after amputation. An amputee having such sensations may still "feel" his or her amputated limb in place. Of particular concern is phantom limb pain, where the amputee 20 feels sensations of pain seemingly arising from the original limb

25 The causes for the often very vivid and disturbing phantom limb sensations reported by a majority of limb amputees are not completely understood, but it is believed that several processes are responsible. Subsequent to loss of normal peripheral sensory nerve input, neurons in

## ARTICLE 34

regions of the cerebral cortex and in particular in the primary sensory cortex associated with the amputated limb can greatly increase their receptivity to synaptic inputs arising from the sensory nerves that remain in the limb stump but are now disconnected from their sensory end-organs.

5

Cortical neurons can also become more receptive to sensory input arising from other regions of the body, in particular from regions that normally project to areas of cortex adjacent to the cortical areas originally dedicated to the amputated limb or body parts. This cortical response process, described as "cortical plasticity" (Ramachandran, V.S., and Hirstein, W. (1998). *The Perception of Phantom Limbs*. The D.O. Hebb lecture. *Brain* 121: 1603-1630), can manifest itself as early as 2 hours after experimental digit nerve amputation in animal models (Merzenich MM, Kaas JH, Wall JT, Sur M, Nelson RJ, Felleman DJ. (1983) *Progression of Change Following Median Nerve Section in the Cortical Representation of the Hand in Areas 3b and 1 in Adult Owl and Squirrel Monkeys*. *Neuroscience* 10(3):639-65); (Kaas JH. (1998) *Phantoms of the Brain*. *Nature* 391(6665):331, 333) and continues to develop for many weeks and months if peripheral nerves remain transected and cannot reestablish contact with their original or other suitable target organs.

It is believed that this greatly increased responsiveness of cortical neurons to inappropriate sensory inputs is at least partly responsible for phantom limb sensations. Phantom limb sensations are thus interpreted to arise from the missing limb or digits, even though the sensations may be triggered by sensory receptors from other body regions or by random activity in the disconnected sensory endings within the amputated limb stump.

5

10

15

20

25

Such phantom limb sensations may or may not include pain components. When pain is present, it is sometimes of such intensity that it becomes unbearable or extremely disabling to the amputee. One possibility which may account for the occurrence of phantom limb pain is that amputation eliminates or greatly disrupts the normal flow of sensory information arising from other modalities of sensory receptors (e.g., low-threshold cutaneous or muscle receptors) carried by larger diameter, myelinated axons. These sensory axons normally convey non-painful information of proprioceptive and cutaneous origin such as touch, pressure, temperature, muscle length, tendon force or joint position.

An important landmark in the pain scientific literature is the work by Wall and Melzack ((1965) *Pain Mechanisms: A New Theory*. Science 150(699):971-9), who in the 1960's proposed the "Gate Control Theory" of pain whereby activity in large diameter touch A<sub>B</sub> nerve fibers were hypothesized to reduce the central transmission of pain activity information carried to the spinal cord by smaller A<sub>D</sub> and C fibers. Although this hypothesis remains controversial, it has brought a focus on the complex interactions that can exist among parallel sensory inputs of different modalities, and on the various central and peripheral factors that can contribute to the central perception of pain. It is now generally accepted that the balance of activity in large and small diameter sensory nerve fibers is important in pain transmission in the spinal cord and brain centers.

In one theory of synaptic connectivity in the central nervous system, proposed by Wall and Melzack, synaptic input from large myelinated sensory fibers normally converge on interneurons that mediate pain

pathway information and tend to inhibit the transmission of pain sensations that are conducted by smaller diameter, unmyelinated sensory nerve fibers. In the absence of proprioceptive and cutaneous information that could inhibit the transmission of pain, the pain pathways are open. The 5 sensations of pain that reach the cortex are interpreted to arise from the missing limb or digits (thus the term "phantom limb" pain), even though the sensations may be triggered by sensory receptors from other body regions, or by random activity in pain afferents in the nerve stumps in the amputated limb or digits.

10

With respect to the fate of nerve fibers in amputated limbs, it is known that all nerve fibers in a severed nerve may atrophy to some extent in the sense that the fiber diameters are reduced, but the nerve cells generally remain viable in the sense that they continue to conduct electrical impulses and retain their basic synaptic connectivity patterns. It is also known that sensory fibers atrophy relatively more than motor fibers (Hoffer, J.A., Stein, R.B. and Gordon, T. (1979) *Differential Atrophy of Sensory and Motor Fibers Following Section of Cat Peripheral Nerves*. Brain Res. 178:347-361) and, furthermore, that large-diameter sensory fibers typically atrophy more than small-diameter sensory fibers. Similarly, large-diameter motor fibers typically atrophy more than small-diameter motor fibers. For hind limb nerves of cats that were cut and ligated over a period of 300 days, Milner et al. ((1981) *The Effects of Axotomy on the Condition of Action Potentials in Peripheral Sensory and Motor Nerve Fibres*. J Neural Neurosurg Psychiatry 44(6):485-96) found that large sensory fibers had a 60% decrease in conduction velocity (CV); small sensory fibers had about a 45% decrease in CV; large motor fibers had a 40% decrease in CV; and small motor fibers had about a 20% decrease in 20 25

CV. Thus, in amputated nerves, "large" and "small" nerve fibers will gradually become closer in their diameters and consequently closer in their thresholds for electrical stimulation.

5        Description of Prior Art

Various pharmacological approaches have been proposed for treating phantom limb pain. Analgesics have generally not worked against this kind of pain. Antidepressant medications can reduce the sensation of pain, but have serious side effects that have limited their applicability. 10 There are currently no approved drugs that are recognized to treat phantom limb pain safely and effectively without unwanted side effects. Another approach, the blockade or removal of the sympathetic supply to the stump, can provide temporary reduction of phantom pain but the effects depend on how soon after amputation the procedure is done, and may not be long-lasting (Livingston KE (1945) *Phantom Limb Syndrome. A Discussion of the Role of Major Peripheral Nerve Neuromas*. J. Neurosurgery 2:251-5).

15

It is known that electrical stimulation of nervous structures can be effective in providing relief of certain types of peripheral pain. Two main approaches used to date are transcutaneous electrical nerve stimulation (TENS) and dorsal column stimulation (DCS) in the spinal cord. It is likely that the mode of action of these therapies involves the stimulation of large diameter sensory fibers in limb nerves (TENS) or in the spinal cord (DCS), 20 reducing the transmission of pain in central pathways described by the Gate Control Theory.

25

5

However, application of these electrical stimulation techniques has had only modest success for treatment of phantom limb pain in amputees. It is likely that TENS ceases to be effective as the sensory fibers in amputated nerves become gradually thinner. As they do so, their electrical thresholds gradually rise, to the point that the fibers can no longer be recruited effectively with TENS.

10

There is some limited evidence that it is possible to selectively stimulate large-diameter sensory fibers in severed nerves of amputees by providing electrical stimulation, thereby eliciting touch sensations without causing any concomitant pain sensations. Stein, R.B., Charles, D., Hoffer, J.A., Arsenault, J., Davis, L.A., Moorman, S. and Moss, B. (1980) *New Approaches to Controlling Powered Arm Prostheses, Particularly by High-Level Amputees*. Bull. Prosth. Res. 17:51-62, showed that it is possible to elicit sensations that the amputee interpreted to arise from an amputated limb, by electrically stimulating sensory axons in a ligated peripheral nerve inside the forearm stump of a below-elbow arm amputee. Even though the arm had been amputated over 30 years earlier, the amputee subject was able to clearly sense the stimulation, which he reported as a non-noxious tingling sensation arising from the ulnar aspect of his phantom limb, specifically from the ring and small fingers which is the sensory field that is normally innervated by the ulnar nerve. The amputee was able to subjectively discriminate frequencies of stimulation ranging from single pulses to steady rates up to 10-20 Hz. For frequencies greater than 20 Hz the sensations were reported as either fused or absent, indicating that the nerve fibers could have been fatigued by high-frequency stimulation in this patient. This reference suggests that severed sensory nerve fibers in

15

20

25

amputees can survive for 30 years or longer in the absence of suitable connections to sensory end-organs.

5 Sculman (U.S. Patent No. 4,232,679) and Schwabe (WO 98/25552) describe systems for providing stimuli to human tissues, but do not have the advantages provided by the present invention.

10

15

20

25

6a

Summary of Invention

This invention provides a system and methods for alleviating phantom limb pain and for replacing lost sensory function from a missing limb.

5

Activity flowing centrally along larger diameter sensory fibers can help suppress the central perception of pain information carried by smaller diameter fibers and, as a corollary, when there is an absence of activity that would normally occur in large diameter sensory fibers, such as in touch receptor afferents that have been disconnected from their peripheral sensory organs, there is a greater chance for pain sensations to reach consciousness. This condition, when it occurs in amputees, for example, may be reversed by selective electrical stimulation of the larger sensory fibers to so restore sensory traffic in these fibers, thus restoring a more normal balance of activity in large and small diameter fibers which will counterbalance again the excessive flow of pain information in central pathways

10

15

Specifically, the invention provides a system for alleviating

20

phantom limb pain which has an implanted electrode or electrodes located in, around or near the severed peripheral nerve stumps that remain inside the proximal stump of an amputated limb. Appropriately chosen electrical stimulation parameters can accomplish the following desirable purposes

- 1) provide sensory feedback about parameters of a prosthetic limb, such as touch, pressure, force, slip, joint position or temperature information; and/or
- 2) provide an effective method of treatment of phantom limb pain.

5

More specifically, the invention provides a system for alleviating phantom limb pain in an amputee having a limb stump, the system comprising a plurality of electrodes implanted in the limb stump, the electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, the electrodes when supplied with electrical current providing electrical stimulation to said nerve; and an electrical signal generator fashioned to communicate varying electrical signals to each electrode. In a preferred embodiment, the electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in the limb stump so as to circumferentially surround a portion of the nerve.

10

15

In a further embodiment, nerve cuff is multi-chambered, and each of the electrodes is segregated into one chamber of the nerve cuff, each electrode thereby being placed in close proximity to a different portion of the nerve.

20  
25 Alternatively, one or more catheters can provide selective delivery of pharmacological agents to the nerve stumps for the treatment of pain

25

5

In one embodiment, the invention has in particular multi-channel interface structures, which may be implanted to permit stimulation of multiple sites or sensory modalities of internal body tissues, such as nerves, together with selective infusion of chemical substances. The interfaces may be provided in the form of nerve cuffs. The interfaces may provide electrical, chemical and/or optical connections to selected bodily tissues.

10

Preferred embodiments of the invention increase the effectiveness of selective recruitment with electrical stimulation of large sensory nerve fibers in severed nerve stumps in amputated limbs by providing electrodes which are implanted inside the amputated limb, directly on or very close to the nerve stumps. Because nerve fibers of different diameters atrophy differently, the thresholds for electrical stimulation of large and small sensory fibers tend to gradually move closer together. Placing the stimulating electrodes closer to the nerve provides an improved means for selectively stimulating the large fibers even after they have atrophied as a consequence of the nerve amputation.

15

20

25

More specifically, the invention provides a system for alleviating phantom limb pain in an amputee having a limb stump, the system comprising a plurality of electrodes implanted in the limb stump, the electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump the electrodes when supplied with electrical current providing electrical stimulation to said nerve, and an electrical signal generator fashioned to communicate varying electrical signals to each

electrode. In a preferred embodiment, the electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in the limb stump so as to circumferentially surround a portion of the nerve.

5                   In a further embodiment, nerve cuff is multi-chambered, and each of the electrodes is segregated into one chamber of the nerve cuff, each electrode thereby being placed in close proximity to a different portion of the nerve. Cuff electrodes are considered to be easier to install and more efficient than other types of electrodes for providing the desired 10 stimulation. Multichannel electrodes are also more efficient for selectively recruiting desired sensory nerve modalities with electrical stimulation. Multi-chambered nerve cuffs are the most preferred design for providing multichannel stimulation.

15                  Another aspect of this invention provides methods of application of non-noxious electrical stimulation of larger, lower-threshold myelinated sensory axons in severed nerve stumps, which may serve to disfacilitate or inhibit the transmission of pain sensations in central pathways. These methods of stimulation may also act to arrest or reduce 20 the evolution of synaptic changes that are believed to occur in the sensory cortex after limb amputation that may be responsible for "phantom limb" sensations, and in particular phantom limb pain sensations.

25

### Brief Description of Drawings

In drawings which illustrate one particular embodiment of the invention,

Figure 1 is a schematic view of an amputee's limb stump and a prosthetic limb equipped with a system for alleviating phantom limb pain and for practising the methods of the invention; and,

Figures 2 and 3 are respectively perspective and cross sectional views of a multi-channel nerve-cuff surrounding a ligated severed nerve in an amputee's stump.

10

### Description

As shown in Fig. 1, the present system for alleviating phantom limb pain in an amputee having a limb stump 10 has a plurality of electrodes 14 (shown in greater detail in Figures 2 and 3) implanted in the limb stump 10, in close proximity to a severed afferent or "sensory" nerve 20 in limb stump 10, which nerve 20 had innervated the amputated limb.

25 In this instance signals communicated by signal generator 12  
to electrodes 14 are preferably transmitted telemetrically in part to avoid

having cabling pass through the amputee's skin. As shown in Figure 1, in the preferred embodiment of the invention signals from signal generator 12 may pass through external cable 18 to transmitting antenna 22A, across the skin of the amputee to receiver antenna 22B, and then through cable 16 to electrodes 14.

As discussed above, each electrode 14 is implanted in limb stump 10 in close proximity to nerve 20. As shown in Figures 2 and 3, nerve 20 may comprise a plurality of nerve fascicles 28 and individual nerve axons 29, all encompassed within the perineurium 27.

It has been determined that electrical signals provided by electrodes 14 to nerve 20 will stimulate or recruit certain portions of nerve 20 (ie. certain neurons), to provide nervous signals, in the form of action potentials, therein. In the context of the description herein, "in close proximity to nerve 20" means that electrodes 14 are implanted in close enough spaced relation to nerve 20 to cause signals to be produced in nerve 20 by transmission of the electrical signals produced by signal generator 12. Accordingly, electrodes 14 may be implanted directly in nerve 20, but may also rest directly on the surface of nerve 20, or may be some small distance away from the surface of nerve 20, as long as the transmission, by electrodes 14, of signals produced by signal generator 12 still causes nervous signals in the form of action potentials to be produced in, and conducted along, nerve 20

25

In a preferred embodiment of the present invention, the electrodes 14 of the system are incorporated within a nerve cuff 30 fashioned to circumferentially surround the nerve 20 when implanted. Such a nerve cuff 30 is shown in greater detail in Figures 2 and 3.

5

As described in Kallesøe et al., U.S. patent No. 5,487,756, and Hoffer et al., U.S. patent No. 5,824,027, both of which are incorporated herein by reference, a nerve cuff is typically a tubular structure having an outer wall which can be used to electrically isolate *in vivo* a tissue of interest, namely a nerve, inside a lumen defined by the cuff wall. Nerve cuffs which are designed to be chronically implanted are made from suitable biocompatible materials such as medical grades of silicone.

10 Nerve cuff 30 may be of any suitable design but as shown in these figures the preferred nerve cuff is a multichannel (ie. it has more than one electrode), multi-chambered nerve stimulation cuff. In a preferred embodiment the various apertures for electrodes 14 and catheters 25, if provided, may be cut in the cuff wall by a laser. The significance of catheters 25 is discussed below.

15

20 Figures 2 and 3 show the preferred nerve cuff of the present invention placed around a severed nerve in an amputated limb. The preferred multichannel nerve cuff 30 has a closure comprising interdigitated tubular members 32 as described in Kallesøe et al. Nerve cuff 30 is closed by running a long member 31 through tubular members 32 when interdigitated.

As taught in the prior art, a plurality of electrodes 14 are placed within individual chambers 23 within nerve cuff 30. Chambers 23 are formed by ridges 24 extending into the lumen of nerve cuff 30. The chambers 23 serve to increase the selectivity of electrical stimulation directed to nerve 20 contained within cuff 30. Specifically, using multichannelled, multi-chambered nerve cuff 30, electrical signals provided by each of electrodes 14 are relatively isolated from one another and a signal from one electrode, or a certain set of electrodes, recruits only specific neurons to produce nervous signals (generally those neurons which are near the specific chamber which hosts the electrode providing the signal). In this manner, selective neurons can be recruited to produce nervous signals by providing signals through particular electrodes.

It will be appreciated that an amputee may appreciate different sensations depending upon which neurons are recruited to send a "sensory signal". If a neuron which had innervated the touch sensors on a fingertip is stimulated, for example, the amputee would have the sensation of this touch.

It has been determined by the present inventor that a plurality of signals may be generated by signal generator 12 and sent to electrodes 14, thereby stimulating various portions of nerve 20. The effect of this, when applied to amputees, is that phantom pain may be alleviated, since the provision of a regular flow of sensory information to the cerebral cortex, and the restoration of a balance of activity in large and small diameter

sensory nerve fibers will tend to inhibit the exaggerated transmission of pain sensations to the sensory brain areas of the amputee.

It has also been discovered that certain patterns of stimulation, generally person-specific, will be more effective than others at alleviating phantom limb pain. In particular, patterns of signals approximating the train of signals received from a normal, innervated limb have been discovered to be particularly effective. In a preferred embodiment of the present invention, the system may be programmed to optimize such stimulation patterns, or the choice of stimulation patterns may be controlled by the amputee. The amputee may adjust the amplitude and frequency of signals, for example, and also may select which channel (ie. electrode) transmits which signal.

In one method, the voltage, current and charge density per stimulation impulse is preferably in the range of 10-1000  $\mu$ s in duration, preferably negative going if monophasic, preferably negative/positive if biphasic, and with current amplitude preferably in the range of 1-10 times the threshold current value for first recruitment of large-diameter sensory fibers, in order to not recruit pain fibers of smaller diameter and higher threshold. Threshold can be determined by the lowest level of stimulation that is detected by the amputee as causing a sensation of cutaneous or proprioceptive modality. Another way to determine the maximum stimulation to be used is by having the amputee report the highest level of stimulation that does not cause a noxious or painful sensation and keeping the stimulation safely below the threshold level for pain.

Further, the preferred method may provide the stimulation in trains in the range up to the maximum frequency that is perceived as non-fused tetani by the amputee, which could be as low as 10-20 Hz or as high as 300 Hz (300 impulses per second). The stimulation can be provided as a constant-frequency train, as regular bursts of constant frequency stimuli, as random bursts, as bursts of gradually increasing/decreasing frequency, or in many other patterns that are determined in part by the reported sensations elicited in the amputee and by the expressed preference of the amputee.

10

15

Again, while the electrical stimulation system of the present invention can be placed anywhere as long as the signals generated can be effectively transmitted to electrodes 14, in a preferred embodiment of the present invention, it is convenient to incorporate signal generator 12 within a prosthetic limb 40, as shown in Figure 1. Prosthetic limb 40 may also be provided with a plurality of sensors 50 (the 3 sensors shown in Figure 1 are labeled 50A, 50B and 50C), and various motors 60.

20

25

As described above, it has been found that the signals sent to nerve 20 to alleviate phantom limb pain are effective when they generally approximate the pattern and train of signals typically seen by the cortex as arising from a normal, innervated limb. It is accordingly desirable to provide a stream of signals to nerve 20 which approximates the normal stream. This can be effectively accomplished by "passing through" signals produced by sensors in the prosthetic limb 40 to nerve 20. Thus, the generator 12 can provide patterns of electrical stimulation to nerve 20 that

depend upon, and approximate, the flow of information to generator 12 from sensors 50 in the prosthetic limb.

In a preferred embodiment, this may be accomplished by  
5 providing a microprocessor in conjunction with signal generator 12 which is programmed to accept signals produced by sensors 50, transducing them to be electrical signals sent to nerve 30 by signal generator 12. The sensory signals from sensors 50 may be telemetered directly from a transmitter in the prosthetic limb to a receiver (not shown) implanted in the  
10 stump, or the transduction may take place in a transducer and transmitter contained in the prostheses. When the prosthetic limb 40 is in use, the sensory feedback system overrides and substitutes for the background activity from the phantom limb pain treatment stimulator described above, which would be switched on at other times (for example, when the amputee  
15 was asleep).

It will be appreciated that the sensory feedback system would operate most effectively if the signals sent to nerve 30 gave the "appropriate" sensation to the amputee upon the activation of a certain sensor in the  
20 prosthetic limb 40. For example, it is much preferred that an amputee get the sensation of a fingertip touching something if the touch sensor on a fingertip of the prosthetic limb 40 is stimulated, than some other sensation, although the cortex will over time adapt at least partially to "inaccurate" sensations. The microprocessor can be programmed to send the appropriate signal to an appropriate electrode 14 depending upon the  
25 particular signal received from a sensor 50. This will simply require

feedback from the amputee about what sensations are felt upon stimulation of different portions of nerve 30 (ie. different electrodes), and the appropriate matches programmed into the microprocessor.

5                   In a further embodiment of the invention, if the system is equipped with a microprocessor, it may be programmed to monitor various voluntary command signals generated by the amputee together with the sensory information flow arriving from sensors 50 in the prosthetic limb 40 and may thus control the action of the motors 60 placed in the prosthetic  
10 limb 40 that control the position and movement of the prosthetic limb joints and digits.

15                   In operation, where the goal is to provide sensory feedback - arising from the prosthetic limb, stimulation preferably will be applied continuously during those periods when the prosthetic limb 40 is connected and in use. When not in use, stimulation may still be applied by signal generator 12 to provide cortical stimulation to keep pain sensation from being interpreted by amputee.

20                   The stimulation will preferably be linked to the intensity of a given sensory input that is being monitored by sensors in the prosthetic limb. For example, for one channel of feedback the monitored input could be grip force, or pressure between the thumb and forefinger. In such case, the intensity of stimulation of the nerve would be graded, within the available dynamic range, to the range of intensities to be monitored. For  
25 example if grip force in the range 0-10 N is to be monitored and the

dynamic range of stimulation frequencies detected by the amputee is 0-20 Hz, then the stimulation could be scaled so that every 1 Hz increment represents an increase of 0.5 N and the stimulation frequency range 0-20 Hz represents the grip force range 0-10 N.

5

For multi-channel systems, essentially similar patterns may be employed, but these can be provided independently to each channel, in such a way that all the stimulation parameters may be different and independently controlled for each channel, and each channel can be dedicated to represent a different sensory modality. For example, if four sensory channels are available for feedback from a hand prosthesis, these can be assigned to represent grip force in the thumb, slip detection in the thumb, angle of the wrist joint, and heat sensed in the palm of the hand. Each of the four sensory inputs would be provided by appropriate sensors built into the prosthetic hand and wrist and would be coded independently as described above for single-channel feedback systems.

It is believed that the systems of the present invention should be implanted as soon as possible following limb amputation (or even before) to provide the greatest benefit, so as to maximally arrest cortical changes subsequent to amputation.

As will be apparent to those skilled in the art in the light of the foregoing disclosure, many alterations and modifications are possible in the practice of this invention without departing from the spirit or scope thereof. For example, it is not critical to the invention to have the electrical

17-08-2001

5

signals produced by a signal generator be transmitted to nerve 20 electrically. The nerve cuff 30 may support the mechanical anchoring of one or more signal transducers, their associated conductors and associated signal processing units. For example, it may be appropriate to have an electrochemical, pharmacological and/or optical system to transduce signals from the signal generator 12 to recruit neurons in nerve 30. Such a pharmacological system 70, which includes catheters 25, is also shown in Figure 1.

10

Further, while the system described herein is described with particular application to amputees, it may also suitably be employed with appropriate modification to work in subjects with other peripheral nerve injuries other than those caused by amputation.

15

Accordingly, the scope of the invention is to be construed in accordance with the substance defined by the following claims.

## WHAT IS CLAIMED IS:

1. A system for alleviating phantom limb pain in an amputee having a limb stump, said system comprising:
  - 5 a) a plurality of electrodes implanted in said limb stump, said electrodes placed in close proximity to a severed sensory nerve in the amputee's limb stump, said electrodes when supplied with electrical current providing electrical stimulation to said nerve; and
  - b) an electrical signal generator fashioned to communicate varying electrical signals to each electrode.
- 10 2. The system as claimed in claim 1 wherein said electrodes are incorporated within a tubular nerve cuff fashioned to be implanted in said limb stump so as to circumferentially surround a portion of said nerve.
- 15 3. The system as claimed in claim 2 wherein said nerve cuff is multi-chambered, and wherein each of said electrodes is segregated into one chamber of said nerve cuff, each electrode thereby being placed in close proximity to a different portion of said nerve
- 20 4. The system as claimed in claim 3 wherein said electrical signal generator is outside of the amputee's body

5. The system as claimed in claim 4 wherein said signals generated by said signal generator are communicated by said generator to said electrodes non-electrically, at least in part.
- 5 6. The system as claimed in claim 5 wherein said signals generated by said signal generator are communicated telemetrically across the skin of the amputee.
- 10 7. The system as claimed in claim 6 wherein said signal generator is contained within a prosthetic limb fashioned to replace the amputee's amputated limb.
- 15 8. The system as claimed in claim 7 wherein said prosthetic limb further comprises a plurality of sensors, each of which provides a sensor signal to said signal generator.
9. The system as claimed in claim 8 wherein said signals produced by said generator are responsive to signals produced by said sensors
- 20 10. The system as claimed in claim 9 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb
- 25 11. A method for alleviating phantom limb pain in an amputee, comprising the steps of

- a) equipping an amputee with the system claimed in any one of claims 1-10; and
- b) providing a stream of nerve stimulation signals to alleviate phantom limb pain, thereby providing a flow of sensory traffic to the cortex.

5

12. A system for providing sensory feedback from a prosthetic limb to an amputee having a limb stump, said system comprising:

- a) a prosthetic limb having a plurality of sensors, each sensor capable of sensing states of touch, or pressure, or force, or slip, or joint position or temperature, each of said sensors producing a unique sensor signal indicative of a sensed state;

- b) a signal transducer contained within said prosthetic limb for transducing each of said unique sensor signals into a unique electrical signal suitable for stimulating action potential activity in nerve fibers;

10

- c) a multi-chambered nerve cuff implanted in said limb stump, said cuff surrounding a severed sensory nerve in said limb stump and incorporating a plurality of electrodes, each of said electrodes when supplied with electrical current providing electrical stimulation to a portion of said nerve, and

15

- d) means for communicating each of said unique electrical signals to a predetermined electrode in said nerve cuff.

20

13 The system as claimed in claim 12 wherein said means for communicating said unique electrical signals comprises electrical and non-electrically signal transmission in combination

25

ARTICLE 34

14. The system as claimed in claim 13 wherein said non-electrically signal transmission comprises telemetric transmission across the skin of the amputee.
- 5 15. The system as claimed in claim 14 wherein a plurality of unique electrical signals are communicated to said electrodes, providing stimulation to said nerve approximating the pattern of stimulation arising from an unamputated, normally innervated limb.
- 10 16. The system as claimed in claim 15 wherein said predetermined electrode, when sent its signal, stimulates that portion of said nerve which provides to the amputee an appropriate sensation.
- 15 17. The system as claimed in claim 12 comprising a plurality of nerve cuffs, each one surrounding a different nerve.
18. A method for providing an amputee with sensory feedback from a prosthetic limb, comprising the steps of:
  - a) equipping an amputee with the system claimed in any one of claims 12-17; and
  - b) providing sensory stimuli to said prosthetic limb.
- 20 19. A system for alleviating pain in a person having a peripheral nerve injury, said system comprising:
  - a) a plurality of electrodes implanted in said person, said electrodes placed in close proximity to an injured sensory nerve in said person,
- 25

said electrodes when supplied with electrical current providing electrical stimulation to said nerve intermediate the site of injury of said nerve and the cortex; and

b) an electrical signal generator fashioned to communicate varying electrical signals to each electrode.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
11 January 2001 (11.01.2001)

PCT

(10) International Publication Number  
WO 01/02054 A2

(51) International Patent Classification<sup>7</sup>:

A61N 1/34

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(21) International Application Number:

PCT/CA00/00789

(22) International Filing Date:

5 July 2000 (05.07.2000)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/142,983 6 July 1999 (06.07.1999) US

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): NEUROSTREAM TECHNOLOGIES, INC. [CA/CA]; 241 Strong Road, Anmore, British Columbia V3H 3C8 (CA).

Published:

— Without international search report and to be republished upon receipt of that report

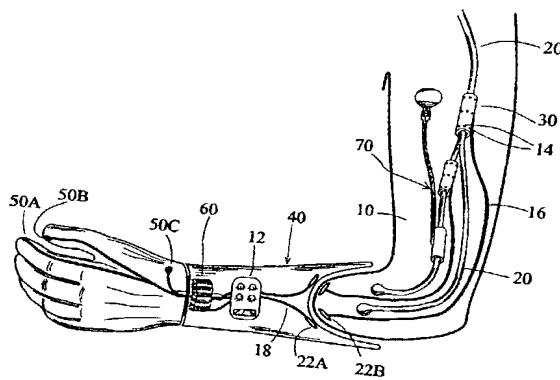
(72) Inventor; and

(75) Inventor/Applicant (for US only): HOFFER, Joaquin, Andres [CA/CA]; 241 Strong Road, Anmore, British Columbia V3H 3C8 (CA).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette

(74) Agent: KONDOR, George, F; Oyen Wiggs Green & Mutala, 480 - 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).

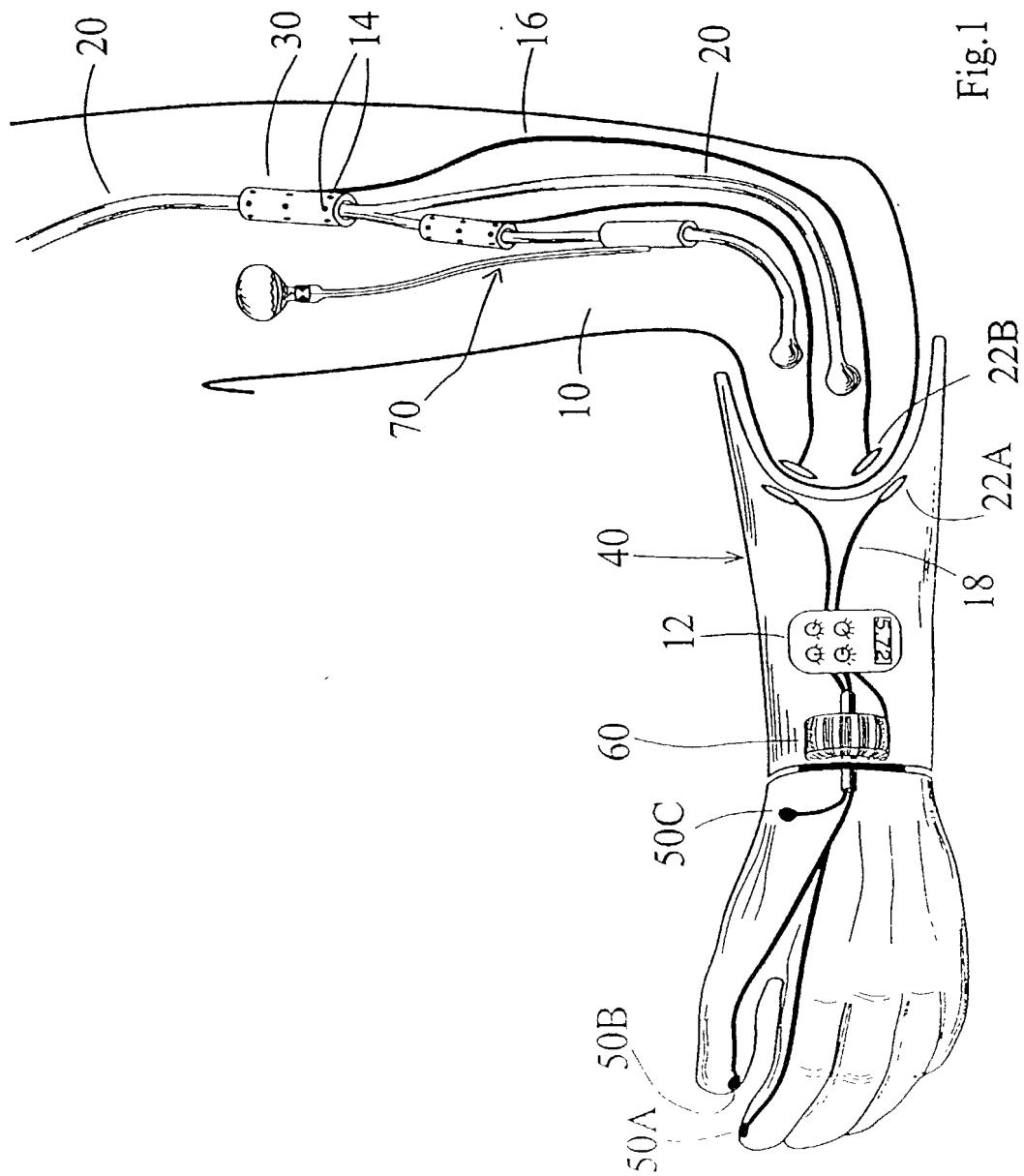
(54) Title: ELECTRICAL STIMULATION SYSTEM AND METHODS FOR TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB



(57) Abstract: This invention relates to a system and methods for relieving phantom limb pain in amputees, and for providing an amputee with sensory feedback from a prosthetic limb. The system employs implantable multichannel, multi-chambered interface structures, namely, nerve cuffs. The implanted nerve cuffs have electrodes which transmit electrical signals generated by a signal generator to nerves, recruiting certain neurons to send sensory signals to the cerebral cortex, suggesting sensory sensations to the amputee. Such signals can arise directly from the signal generator, approximating the train of signals seen by the cortex in a normally innervated limb, or can originate from sensors in a prosthetic limb.

WO 01/02054 A2

1/3



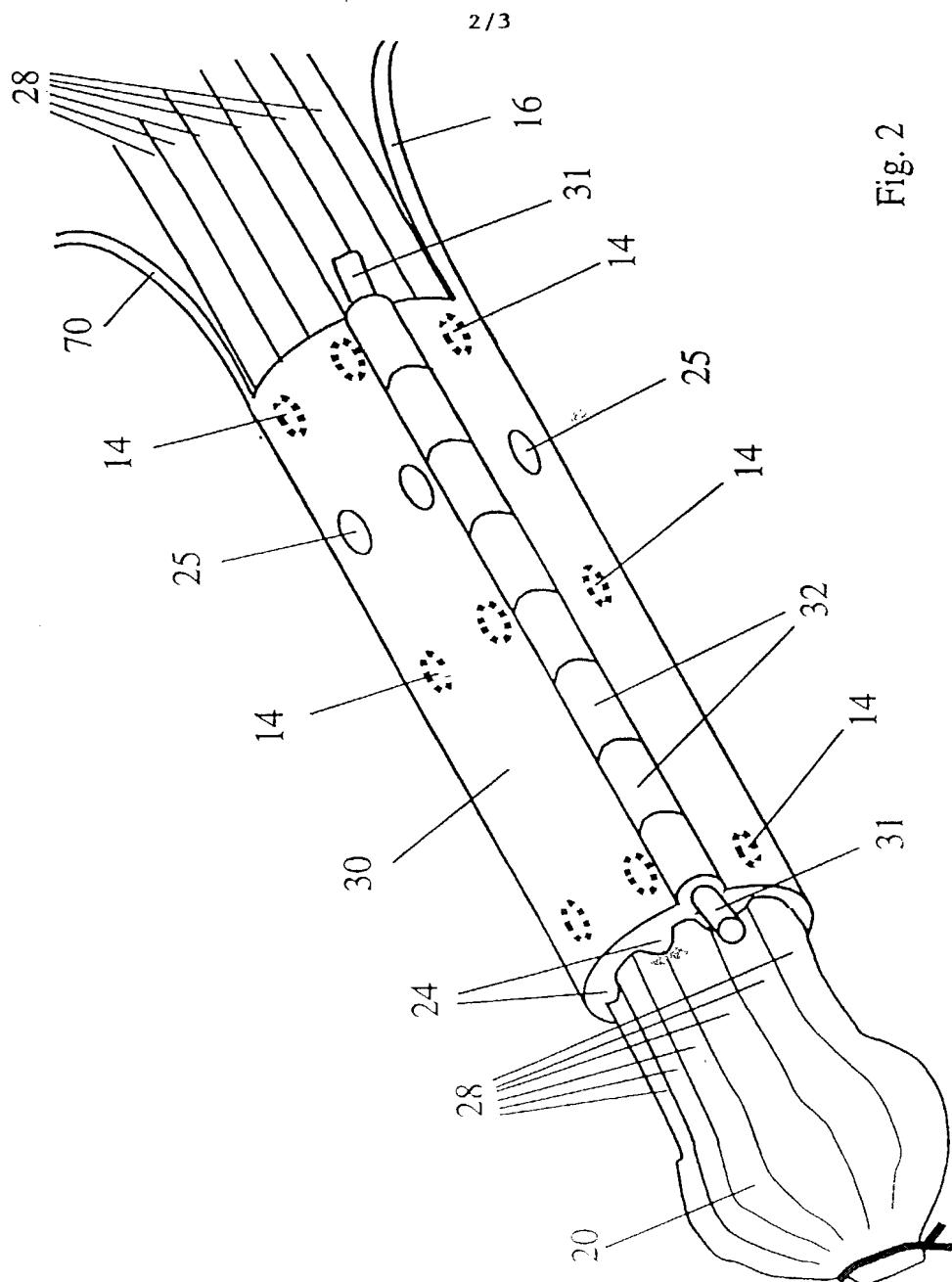


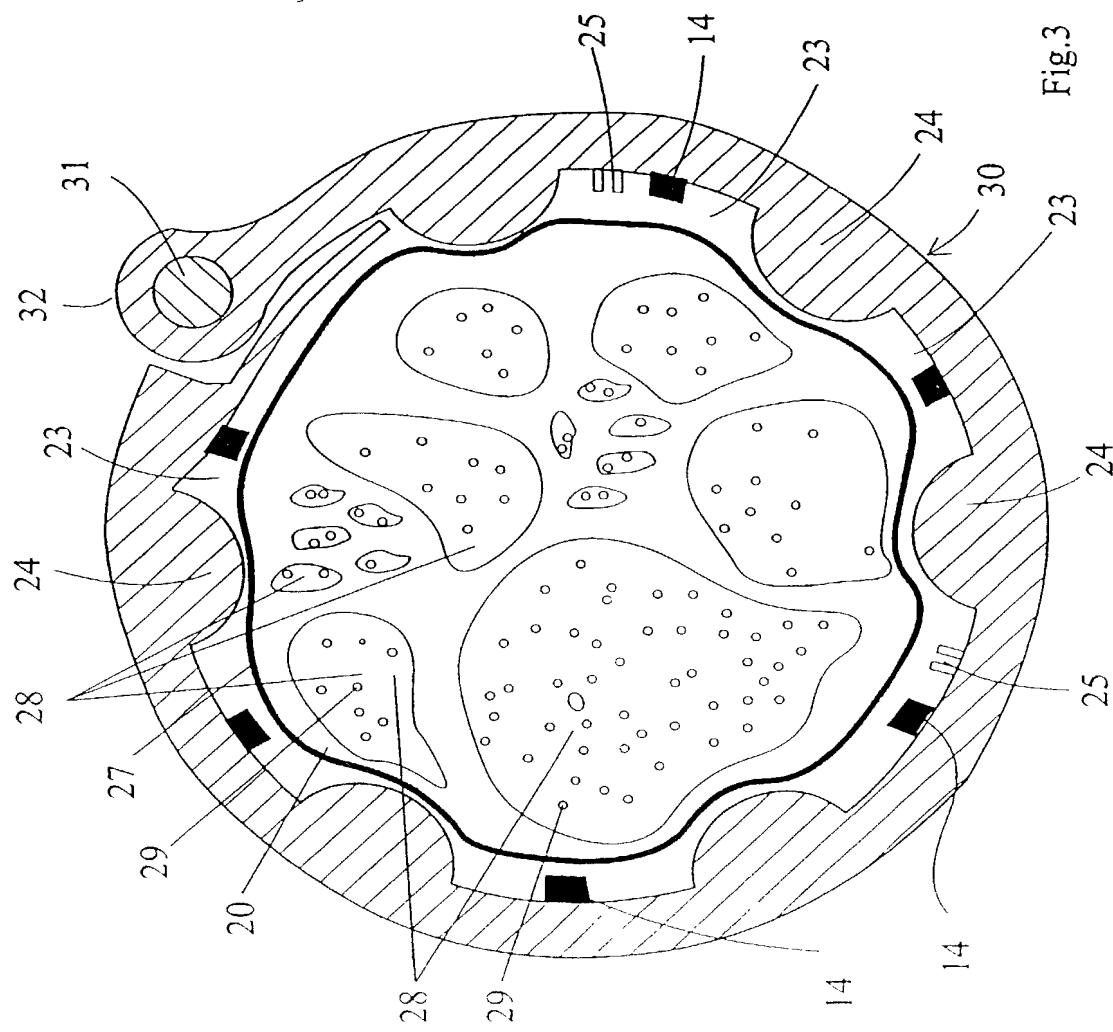
Fig. 2

10/030973

WO 01/02054

PCT/CA00/00789

3/3



SUBSTITUTE SHEET (RULE 26)

**COMBINED DECLARATION AND POWER OF ATTORNEY  
FOR PATENT APPLICATION**

As a below named inventor, I hereby declare that.

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled ELECTRICAL STIMULATION SYSTEM AND METHODS FOR TREATING PHANTOM LIMB PAIN AND FOR PROVIDING SENSORY FEEDBACK TO AN AMPUTEE FROM A PROSTHETIC LIMB, the specification of which

- is attached hereto.
- was filed on January 4, 2002 as United States Patent Application No. 10/030,973
- was described and claimed in PCT International Application No. PCT/CA00/00789, filed on 5 July 2000, and as amended under PCT Articles 19 on \_\_\_\_\_ (if applicable).
- and was amended on \_\_\_\_\_ (if applicable).
- with amendments through \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above

I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. § 1.56. If this is a continuation-in-part application filed under the conditions specified in 35 U.S.C. § 120 which discloses claims and subject matter in addition to that disclosed in the prior copending application, I further acknowledge the duty to disclose material information as defined in 37 C.F.R. § 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the applications(s) on which priority is claimed.

<hr/> Number	<hr/> Country	<hr/> Day/Month/Year Filed	<input type="checkbox"/>	<input type="checkbox"/>
			Yes	No

I hereby claim the benefit under 35 U.S.C. § 119(e) of any United States provisional application(s) listed below.

<hr/> Application Number	<hr/> Filing Date
60/142,983	6 July 1999

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) or § 365(c) of any PCT international application(s) designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

<hr/> Application Number	<hr/> Filing Date	<hr/> Status: patented, pending abandoned
--------------------------	-------------------	---

I hereby appoint the practitioners associated with the customer number provided below to prosecute this application, to file a corresponding international application, and to transact all business in the Patent and Trademark Office connected therewith:

Customer Number



**24197**  
Klarquist Sparkman

Name	Reg. No.	Name	Reg. No.
BUNKER, Gillian	47,461	ORR, David E.	44,988
BURG, Daniel B.	41,649	PETERSEN, David P.	28,106
CALDWELL, Lisa M.	41,653	POLLEY, Richard J.	28,107
CARLSON, Anne	47,472	RINEHART, Kyle B.	47,027
GIRARD, Michael P.	38,467	RUPERT, Wayne W.	34,420
HAENDLER, Jeffrey B.	43,652	RYBAK, Sheree L.	47,913
HARDING, Tanya M.	42,630	SCOTTI, Robert F.	39,830
JAKUBEK, Joseph T	34,190	SIEGEL, Susan Alpert	43,121
JONCUS, Stephen J.	44,809	SLATER, Stacey C	36,011
JONES, Michael D.	41,879	STEPHENSON Jr, Donald L.	34,022
KLARQUIST, Kenneth S.	16,445	STUART, John W.	24,540
KLITZKE II, Ramon A.	30,188	VANDENBERG, John D.	31,312
LEIGH, James S.	20,434	WHINSTON, Arthur L	19,155
MC LEOD, Richard D	46,921	WIGHT, Stephen A.	37,759
MAURER, Gregory L	43,781	WINN, Garth A.	33,220
MIRHO, Charles A.	41,199	ZASTROW, Devon J.	50,206
NOONAN, William D.	30,878		

I hereby grant the law firm of Klarquist Sparkman, LLP, the power to insert on this Combined Declaration and Power of Attorney any further identification which may be necessary or desirable in order to comply with the rules of the United States Patent and Trademark Office for submitting this document.

Address all telephone calls to Robert F. Scotti at telephone number (503) 226-7391.

Address all correspondence to the address associated with the customer number provided below:

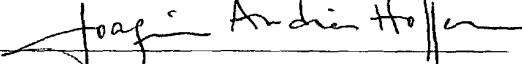
Customer Number



**24197**  
Klarquist Sparkman

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

1-00

Name of First or Sole Inventor:	Joaquin Andres Hoffer
Residence:	Anmore, British Columbia, CANADA CAX 5E9
Mailing Address:	241 Strong Rd., Anmore, BC, V3H 3C8 CANADA
Citizenship:	Canada
Inventor's Signature	
	Date 15 May 2002